

ALL INFORMATION CONTAINED HEREIN IS UNCLASSIFIED  
DATE 11/19/01 BY 60322 UCBAW

Certificate of Mailing by Express Mail (37 CFR 1.10)

Express Mail Mailing Label Number: EV 063 566 415 US Mailing Date: May 22, 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Commissioner of Patents and Trademarks, Box Missing Parts, Washington, D.C. 20231.

*Cindy Wilson*  
Cindy Wilson

Patent  
Attorney Docket: P-011-RC2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	)	
	)	
Burton G. Christensen et al.	)	Group Art Unit: 1627
	)	
Application No.: 10/015,534	)	
	)	Examiner: Unassigned
Filed: December 13, 2001	)	
	)	
For: Methods for Identifying Novel	)	
Multimeric Agents that Modulate	)	
Receptors	)	

**RESPONSE TO NOTICE OF MISSING PARTS**  
**and PRELIMINARY AMENDMENT**

BOX MISSING PARTS  
Assistant Commissioner for Patents  
Washington, DC 20231

Dear Sir:

This reply is being submitted in response to the Notice to File Missing Parts mailed on March 25, 2002, for the above-identified application. This notice set a two-month period for response, the due date of which falls on Saturday, May 25, 2002. Since Monday, May 27, 2002 is a federal holiday (Memorial Day), this paper is considered timely filed if submitted on or before Tuesday, May 28, 2002.

In addition to responding the Notice to File Missing Parts, Applicants also respectfully request entry of the following preliminary amendments prior to examination of this application on the merits.

In the Specification:

On page 1, at lines 7-10, please delete the paragraph directly below the heading "Cross-Reference to Related Applications", and insert in place thereof the following paragraph:

This application is a continuation of U.S. Serial No. 09/493,462, filed on January 28, 2000 (now abandoned); which application is a continuation of U.S. Serial No. 09/327,904, filed on June 8, 1999 (now abandoned); which application claims the benefit of U.S. Provisional Application Serial No. 60/092,938, filed July 15, 1998; and U.S. Provisional Application Serial No. 60/088,466, filed on June 8, 1998; which applications are incorporated herein by reference in their entirety.

On page 157, at lines 6-10, please delete the paragraph at lines 6-10, and insert in place thereof the following paragraph:

The AT1 receptor has a small molecule antagonist binding site and a peptide agonist binding site which are partially overlapping. There is an overlap between the propylimidazole and biaryl tetrazole motifs with the side chains of the fifth, sixth, seventh and eighth amino acids (i.e., isoleucine, histidine, proline and phenylalanine) and the terminal carboxylate in the N-terminus of the angiotensin II peptide.

In the Claims

Please delete Claims 1-35 without prejudice or disclaimer.

Please add Claims 36-40 as follows:

36. (Newly Added) A method of preparing a library of compounds of the formula:

L-X-L

wherein

each L is independently a ligand which binds to a cellular receptor; and

X is a linker of the formula:

-X'-Z-(Y'-Z)<sub>m</sub>-Y''-Z-X'-



wherein

$m$  is an integer of from 0 to 20;

$X'$  at each separate occurrence is selected from the group consisting of -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH- and a covalent bond;

$Z$  at each separate occurrence is selected from the group consisting of alkylene, cycloalkylene, alkenylene, alkynylene, arylene, heteroarylene, heterocyclene and a covalent bond;

$Y'$  and  $Y''$  at each separate occurrence are selected from the group consisting of -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -NR'-C(O)-O-, -P(O)(OR')-O-, -S(O) <sub>$n$</sub> CR'R"-, -S(O) <sub>$n$</sub> -NR'-, -S-S- and a covalent bond; where  $n$  is 0, 1 or 2; and

$R'$  and  $R''$  at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

the method comprising the steps of:

(a) identifying a ligand compound which binds to a cellular receptor;

(b) providing a plurality of functionalized ligand compounds, each functionalized ligand compound comprising the ligand compound from step (a) having a reactive functional group selected from the group consisting of an -NH<sub>2</sub>, COOH, C(O)Y, CHO, OH, SH, N=C=O and Y group, where Y is halo; wherein the reactive functional group of each functionalized ligand compound is located at a different position relative to the other functionalized ligand compounds;

(c) providing a linker compound comprising two reactive functional groups independently selected from the group consisting of an -NH<sub>2</sub>, -COOH, -C(O)Y, -CHO, -OH, -SH, -N=C=O and -Y group, where Y is halo; wherein each of the reactive function groups of the linker compound has complementary reactivity to the reactive functional group of a functionalized ligand compound from step (b);

(d) reacting the linker compound from step (c) with each of the functionalized ligand compounds from step (b) to provide a library of compounds of the formula L-X-L.

37. (Newly Added) The method of Claim 36, wherein the method further comprises the step of:

(e) assaying each compound of the library from step (d) to determine its affinity for the cellular receptor.



38. (Newly Added) The method of Claim 36, wherein the linker compound has a chain length between reactive functional groups of from about 2 Å to 100 Å.

39. (Newly Added) The method of Claim 36, wherein the cellular receptor is a G-protein coupled receptor.

40. (Newly Added) The method of Claim 39, wherein the cellular receptor is a muscarinic receptor.



### REMARKS

Entry of the above amendments and consideration of the following remarks is respectfully requested.

#### 1. Status of the Claims

Claims 1-35 have been canceled and new Claims 36-40 have been substituted in place thereof. Accordingly, Claims 36-40 are now pending for examination on the merits.

#### 2. Summary of the Amendments

The specification has been amended on page 1 to include further information on related applications. The specification has also been amended on page 157, at line 6-10, to delete the recited four amino acid sequence, i.e., Ile5-His6-Pro7-Phe8, and to recite in place thereof a general description of this sequence.

Additionally, Claims 1-35 have been canceled without prejudice or disclaimer. Applicants specifically reserve the right to pursue the subject matter of these cancelled claims in a continuation application.

New Claims 36-40 have been added. Support for these newly added claims is found, for example, in the following locations of the application as originally filed:

For Claim 36: On page 43, lines 14 through page 44, line 10; page 44, lines 19-22; page 86, lines 20-23; page 88, line 4 through page 89, line 8; and page 99, line 26 through page 109, line 7.

For Claim 37: On page 75, line 29 through page 76, line 4; page 106, line 27 through

page 107, line 6; page 139, line 1 through page 145, line 16; page 163, line 1 through page 164, line 14; and page 172, line 8 through page 173, line 14.

For Claim 38: On page 44, lines 11-18; and page 74, lines 20-21.

For Claim 39: On page 10, line 5 through page 21, line 6.

For Claim 40: On page 31, lines 27-28; page 65, lines 17-18; page 65, line 22 through page 66, line 11; page 145, line 21 through page 155, lines 27; and Figs. 24 and 25.

Entry of the above amendments is respectfully requested. Pursuant to 37 C.F.R. §1.121, a marked-up version showing the changes made to the specification is attached.

### 3. Substitute Specification

A Notice to File Missing Parts was mailed on March 25, 2002, for this application (copy enclosed herewith). This Notice indicated that a substitute specification was required in compliance with 37 C.F.R. §1.52, because the submitted papers allegedly contained improper margins.

In response, a substitute specification is submitted herewith in which each sheet of the specification has a left margin of at least 2.5 cm and top, bottom and right margins of at least 2.0 cm. Additionally, the table found on pages 110-115 of the specification has been redrawn for increased legibility and reproducibility. Additional pages have been numbered as 110a-e, 111a-f, 112a-b, 113a-e, 114a-e, and 115a-b.

### 4. Substitute Drawings

The Notice to File Missing Parts also indicated that substitute drawings were required in compliance with 37 C.F.R. §1.84, because the submitted drawings allegedly contained improper margins.

In response, substitute drawings are submitted herewith in which each sheet has a top and left side margin of at least 2.5 cm, a right side margin of at least 1.5 cm and a bottom margin of at least 1.0 cm.

### 5. Compliance with Sequence Listing Requirements of 37 C.F.R. §§1.821-1.825

The Notice to File Missing Parts also indicated that a Sequence Listing was required for this application in compliance with 37 C.F.R. §§1.821-1.825.

In response, Applicants have amended page 157, at line 9, to delete the recited four amino acid sequence, i.e., Ile5-His6-Pro7-Phe8. Accordingly, in view of this amendment, no Sequence Listing is required for this application.

6. Payment of Filing Fees

This application was filed without the statutory basic filing fee and the Notice to File Missing Parts has indicated that fees are now due. Applicants respectfully request that the fees be calculated in view of the above amendments which reduce the total number of claims to five (5) and the number of independent claims to one (1). Accordingly, payment of these fees and the Missing Parts surcharge are authorized in the Missing Parts transmittal accompanying these documents.

7. Request To Correct Filing Receipt

A Request to the Correct Filing Receipt for this application is being submitted herewith. Appropriate correction of the Filing Receipt is respectfully requested.

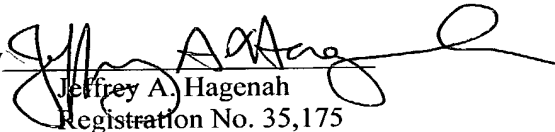
8. Information Disclosure Statement

In accordance with the duty of disclosure set forth in 37 C.F.R. §1.56, Applicants enclose an Information Disclosure Statement and a modified form PTO-1449 listing documents for consideration by the Examiner. Applicants respectfully request that an Examiner initialed copy of this form be returned to the undersigned.

In view of the above, Applicants believe this application is now ready for examination on the merits and early examination is respectfully requested. Should there be any questions concerning this response, the undersigned Attorney for Applicants can be reached at (650) 808-6406.

Respectfully submitted,

Date 5-22-02

By   
Jeffrey A. Hagenah  
Registration No. 35,175

Theravance, Inc.  
(formerly Advanced Medicine, Inc.)  
901 Gateway Boulevard  
South San Francisco, CA 94080  
650/808-6000 Telephone  
650/808-6078 Fax

VERSION WITH MARKINGS TO SHOW CHANGES MADE

On page 1 of the specification, lines 7-10, the paragraph directly below the heading "Cross-Reference to Related Applications" has been amended as follows:

This application is a continuation of U.S. Serial No. 09/493,462, filed on January 28, 2000 (now abandoned); which application is a continuation of U.S. Serial No. 09/327,904, filed on June 8, 1999 (now abandoned); which application claims the benefit of U.S. Provisional Application Serial No. 60/092,938, filed July 15, 1998; and U.S. Provisional Application Serial No. 60/088,466, filed on June 8, 1998; which applications are incorporated herein by reference in their entirety. This application claims priority to U.S. Provisional Application Serial No. 60/092,938, filed July 15, 1998 and U.S. Provisional Application Serial No. 60/088,466, filed on June 8, 1998, both of which are incorporated herein in their entirety by reference.

On page 157, the paragraph on lines 6-10 has been amended as follows:

The AT1 receptor has a small molecule antagonist binding site and a peptide agonist binding site which are partially overlapping. There is an overlap between the propylimidazole and biaryl tetrazole motifs with the side chains of the ~~He5-His6-Proo7-Phe8~~ fifth, sixth, seventh and eighth amino acids (i.e., isoleucine, histidine, proline and phenylalanine) and the terminal carboxylate in the N-terminus of the angiotensin II peptide.